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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/680,208	10/06/2000	Harold A. Robertson	36541-0005	8654

7590 07/01/2003

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/680,208	ROBERTSON ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 October 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0801* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed 9/20/02. Currently, claims 1-20 are pending. Claims 1-13, 20 have been withdrawn as drawn to non-elected subject matter.

2. Claims 15-19 have been examined on the merits.

Election/Restrictions

3. Applicant's election of Group IV on April 25, 2002 is acknowledged. The response asserts that there is a unity of invention among these groups of claims. It is noted that the instant application is not a 371 application. Therefore, the unity of invention standard does not apply to this application. Rather, restriction practice is appropriate which requires a showing of patentably distinct inventions.

The traversal is on the ground(s) that restriction is only required when the inventions are independent and distinct. This is not found persuasive because dependent inventions may be properly restricted if they are distinct. As discussed in MPEP 803, one of the two criteria for requirement of restriction is that the "inventions must be independent (see MPEP 802.01, 806.04, 808.01) or distinct as claimed". Accordingly, the demonstration of distinctness of the inventions is sufficient grounds for restriction. As stated in MPEP 802.01 "(t)he law has long been established that dependent inventions (frequently termed related inventions) such as those used for illustration above may be properly divided if they are, in fact "distinct" inventions, even though dependent".

Applicants further argue that it would not be an undue burden to examine the claims of all groups I-IV. However, it is maintained that undue burden would be required to examine the claims of groups I, II, III, along with the claims of group IV as evidenced by the fact that the claims of groups I, II, III and IV have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter and because a search of the subject matter of invention IV is not co-extensive with a search of inventions I-III.

The election of a particular disorder has been withdrawn in view of the applicant's arguments and further reconsideration.

Newly added Claim 20 has been restricted from Group IV because Group IV is drawn to a nucleic acid detection method, classified in 435/6. However, newly added Claim 20 is drawn to a protein assay, classified in 435/7.1. The methods are patentably distinct methods because they are drawn to detecting different products.

During a telephone conversation with David Heller on June 17, 2003 a provisional election was made with traverse to prosecute the invention of Group IV (drawn to nucleic acid detection methods), claims 15-19. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-14, 20 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 1-13, 20 drawn to an invention nonelected with traverse. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

4. This application claims priority to provisional applications 60/158,043 and 60/217,765, filed October 7, 1999 and July 12, 2000, respectively.

Drawings

5. The drawings are objected to.

6. Figure 3 fails to identify the sequence by a sequence identifier, either on the figure or in the brief description of the figures.

7. Figure 7 contains panels A-D, however, the brief description of the drawings fails to describe each of these figures.

Information Disclosure Statement

8. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The list of references appears on pages 66-71 of the specification.

Sequence Rules

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

It is noted that several sequences have been provided in the specification which have not been identified by a sequence identifier. For example, sequences lacking sequence identifiers on pages 44, 46, 49 and 50 of the specification.

Specification

10. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method for detecting the presence of or the predisposition for a CAG repeat disorder by determining the expression of RNA corresponding to PDE10A in an individual.

The specification specifically states that "PDE10" comprises a polynucleotide sequence which is down regulated in the course of CAG repeat disorders selected from the group consisting of: (a) a sequence comprising SEQ ID NO:1 ; (b) a sequence comprising SEQ ID NO:2; (c) a sequence comprising SEQ ID NO:1 1; (d) a sequence comprising nucleotides 257 to 2596 of SEQ ID NO:1 1; (e) a sequence which is at least 90% homologous with a sequence of (a), (b), (c) or (d), and; (f) a sequence which hybridizes to (a), (b), (c) or (d) under stringent conditions. The specification further continues to define the invention as to encompass polynucleotides that are at least 70% identical over the entire length to a polynucleotide encoding PDE10 (page 13-14). The specification also appears to state that SEQ ID NO: 12 is the nucleotide sequence of cPDE10A (page 8).

The specification provides a sequence for PDE10A from the mouse. SEQ ID NO: 12 is PDE10A of the mouse.

The art teaches a homo sapiens mRNA for 3',5'-cyclic nucleotide phosphodiesterase, PED10-1 (Genbank Accession Number AB020593, June 1999). The nucleic acid of Omori and SEQ ID NO: 12 are 23.6% similar. The art also teaches the rattus norvegicus mRNA for PDE10A2 which is 34.4% similar to SEQ ID NO: 12 (Genbank Accession Number AB027155, January 7, 2000).

Soderling et al. (herein referred to as Soderling) teaches the cloning, expression and characterization of a PDE10A from mouse (PNAS, Vol. 96, pages 7071-7076, June 1999). Soderling teaches PDE10A represents a previously unrecognized means by which cyclic nucleotides are likely to be regulated in both mouse testis and brain (page 7076).

Fujishige et al. (Eur. J. Biochem. Vol. 266, pages 1118-1127, December 1999) teaches PDE10A cloned and investigated in rats. The deduced amino acid sequence of one of the major variant forms contained 794 amino acids and was 96% identical to human PDE10A2. Figure 2 provides an alignment of rat and human PDE10A2. Figure 3 provides a further comparison of the N-terminal amino acid sequences of rat and human PDE10A (page 1122).

Moreover, the art teaches the genomic structure of the human PDE10A gene and the organization of several splice variants of PDE10A (Fujishige et al. Eur. J. Biochem. Vol. 267, pages 5943-5951, October 2000). Fujishige teaches the presence of six possible PDE10A splice variants having distinct N-and C-termini (page 5944, col. 1). As seen in Figure 2B, the 6 various splice variants contain different combinations of N and C termini (page 546).

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from

its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, prior to the filing date, Applicant has defined only a small number of PDE10A nucleic acids which fall within the scope of the claims. The specification has not provided sequences which are 90% homologous with SEQ ID NO: 1, 2, 11 or positions 257-2596 of SEQ ID NO: 11. Moreover, the specification fails to describe a representative number of sequences which hybridize under stringent conditions to SEQ ID NO: 1, 2, 11 or nucleotides 257-2596. The claims would encompass, not only splice variants, but also SNPs, mutations, deletions, and homologous sequence from additional organisms.

With respect to hybridization language, a person of skill in the art would expect substantial variation among species encompassed within the scope of the claims. The

claim does not specify any stringency conditions. The claim is broad and read on virtually any nucleic acid. While there are three species disclose, SEQ ID NO: 1, 2, 11, the art indicates that there is substantial variation within the genus because the lack of stringency of hybridization conditions would be expected to yield structurally unrelated nucleic acid molecules. The disclosed species are not representative of the genus because there is no structural attribute or feature which is common to the members of the genus. Applicant has not disclosed any of the several splice variants of PDE10A, the genomic PDE10A and particularly has not disclosed any intron sequences or regulatory sequences. Following the filing of the instant application, Fujishige has provided a complete analysis of PDE10A which illustrates that the PDE10A gene spans more than 200kb and contains 24 exons. Furthermore, six splice variants of PDE10A have been described in the art after filing of the instant application.

Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for detecting the presence of or the predisposition for a CAG repeat disorder by determining the expression of RNA corresponding to PDE10A in an individual wherein the decreased expression of PDE10A as compared to a control is indicative of a CAG repeat disorder.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The specification teaches that human PDE10 was recently identified by Loughney (WO 99/42596). The specification teaches that "PDE10 was found to share homology with known PDEs, no function could be identified for PDE10." (page 4 of specification). The specification provides a sequence for PDE10A from the mouse. SEQ ID NO: 12 is PDE10A of the mouse. The specification specifically states that "PDE10" comprises a polynucleotide sequence which is down regulated in the course of CAG repeat disorders selected from the group consisting of: (a) a sequence comprising SEQ ID NO:1 ; (b) a sequence comprising SEQ ID NO:2; (c) a sequence comprising SEQ ID NO:1 1; (d) a sequence comprising nucleotides 257 to 2596 of SEQ ID NO:1 1;

(e) a sequence which is at least 90% homologous with a sequence of (a), (b), (c) or (d), and; (f) a sequence which hybridizes to (a), (b), (c) or (d) under stringent conditions. The specification further continues to define the invention as to encompass polynucleotides that are at least 70% identical over the entire length to a polynucleotide encoding PDE10 (page 13-14). All of the analysis in the instant specification is directed to mice. There are not examples directed to human CAG repeat disorders of human PDE10A. The specification asserts that Figure 2 demonstrates that PDE10A is expressed in the striatum but not the cortex of wild-type mice and the steady-state levels of PDE10A are reduced in 10 week old transgenic HD mice. The specification states that "the hybridization signal of pPDE10A was significantly lower in the RNA samples derived from the striatum of 10 week-old HD mice." (page 48). The specification states that PDE10A was found to "have extremely high homology with human PDE10s identified by Loughney (WO 99/42596)(page 50). The specification, however, fails to provide any alignment or information with respect to the "extremely high homology." Moreover, it is unclear whether the homology is over the entire length of the nucleic acid or whether the homology is only over a particular domain. The specification also provide an in situ hybridization assay which "confirmed the northern blot analysis" which demonstrated that the levels of PDE10A mRNA were decreased in HD mice compared to the wild-type (page 51). The specification states that "in mouse, PDE10A mRNA was detected in testis and to a much lesser extend in brain" (page 59). Moreover, the specification states that "in humans, PDE10A is expressed in the caudate, putamen and testis." (page 59).

The art teaches a homo sapiens mRNA for 3',5'-cyclic nucleotide phosphodiesterase, PED10-1 (Genbank Accession Number AB020593, June 1999). The nucleic acid of Omori and SEQ ID NO: 12 are 23.6% similar. The art also teaches the rattus norvegicus mRNA for PDE10A2 which is 34.4% similar to SEQ ID NO: 12 (Genbank Accession Number AB027155, January 7, 2000).

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Moreover, the art teaches the genomic structure of the human PDE10A gene and the organization of several splice variants of PDE10A (Fujishige et al. Eur. J. Biochem. Vol. 267, pages 5943-5951, October 2000). Fujishige teaches the presence of six possible PDE10A splice variants having distinct N-and C-termini (page 5944, col. 1). As seen in Figure 2B, the 6 various splice variants contain different combinations of N and C termini (page 546).

Neither the art nor the specification teaches the skilled artisan how to make and use the claimed invention as broadly as claimed. The specification and the claims of the instant application assert that detection of a decreased expression of PDE10A as compared to a predetermined control level of expression allows for the detection of the presence or predisposition for a CAG repeat disorder.

The specification fails to provide any guidance as to the scope of CAG repeat disorders. While the specification, page 28, provides a list of triplet-repeat disorders which includes schizophrenia, stroke, trauma, Parkinson's disease and Alzheimer's disease (AD). However, this list does not appear to be a complete list of triple-repeat disorders. Furthermore, it is unclear whether CAG repeat disorders differ from triplet-repeat disorders. The claims appear to suggest that a CAG repeat disorder encompasses Huntington's disease, however, Huntington's disease does not appear to be listed as a triplet-repeat disorder. Spinocerebellar Ataxias are also CAG repeat disorders which do not appear on the list of disorders. Therefore, the use of CAG repeat disorders is a very broad class of disorders. Each of these disorders is diverse and there does not appear to be any particular link between structure and function of the diseases. For example, SCA2 is caused by an increase in CAG repeats. For example, normal individuals generally have 21 CAG repeats in SCA2 where as diseased individuals have more than 35 CAG repeats. Thus, CAG repeat disorders to not all appear to be related, since SCA2 is not affected by expression levels. Therefore, detecting any CAG repeat disorder based solely on different sample expression would be unpredictable. While one could conduct additional experimentation to determine

whether, e.g., decreased expression of PDE10A might be associated with e.g., various CAG repeat disorders, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. Furthermore, the teachings of the prior art doe not provide evidence of how to use the methods in which expression of PDE10A or genes which are 90% or hybridize to PDE10A are indicative of a CAG repeat disorder. Based upon the specification it is unclear which nucleic acids have been used in the analysis of the Huntington's disease. The specification appears only to teach SEQ ID NO: 1, 2, 11, 12 which are mouse sequences. The specification fails to provide any human sequences. Moreover, post filing date, the art has provided evidence that there are at least 6 splice variants of the human PDE10A sequence. The instant specification does not teach any analysis of these splice variants of PDE10A. It is further unpredictable where all of the splice variants function in the same manner to affect the expression level to cause a CAG repeat disorder. It is unpredictable whether each of the PDE splice variants from the human are expressed in the same manner. The specification states that "in mouse, PDE10A mRNA was detected in testis and to a much lesser extend in brain" (page 59). Moreover, the specification states that "in humans, PDE10A is expressed in the caudate, putamen and testis." (page 59). Moreover, based upon the extremely broad definition of PDE10A nucleic acids in the specification, the claim encompasses variants. These variants may include variants which afford a protective effect to the nucleic acid such that they are indicative of a lower risk for CAG repeat disorder. These further variations may also include SNPs, mutations, deletions, insertions, homologous

sequences from additional organisms which may have different diagnostic implications in the nucleic acids. Without further unpredictable experimentation, the skilled artisan would not be aware of which of the variants would have which effects on the presence or predisposition of CAG repeat disorders. Therefore, it is unclear that all PDE10A nucleic acids have the same means and levels of expression. While one could conduct additional experimentation to determine whether, e.g., expression of each of the human splice variants might be associated with, e.g., certain CAG repeat disorders, the outcome of such research cannot be predicted, and such further research and experimentation are both unpredictable and undue. It is unpredictable as to whether any quantity of experimentation would allow one to practice the claimed invention.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 15-19 are indefinite over the recitation "corresponding to" because it is unclear what type of relationship corresponding imparts. It is unclear whether corresponding is used in the sense that "determining the level of expression of RNA of PDE10A" is intended; whether the claim is directed to a method of detecting DNA which corresponds to RNA; or whether the claim is drawn to determining the level of

expression of RNA of a distinct nucleic acid which may have some relationship to PDE10A, without actually detecting PDE10A.

Conclusion

14. No claims allowable.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
June 25, 2003

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